DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our STN: BL 125019/0

FEB 19 2002

Ms. Alice Wei
IDEC Pharmaceuticals Corporation
3030 Callan Road
San Diego, CA 92121

Dear Ms. Wei:

Your biologics license application for Ibritumomab Tiuxetan is approved effective this date. IDEC Pharmaceuticals Corporation, San Diego, California, is hereby authorized to introduce or deliver for introduction into interstate commerce, Ibritumomab Tiuxetan and associated components for the preparation of Indium-111 Ibritumomab Tiuxetan and Yttrium-90 Ibritumomab Tiuxetan under Department of Health and Human Services U.S. License No. 1235.

Ibritumomab Tiuxetan, as part of a specific therapeutic regimen, is indicated for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma, including patients with Rituximab (Rituxan™) refractory follicular non-Hodgkin's lymphoma. The therapeutic regimen includes Rituximab, Indium-111 Ibritumomab Tiuxetan, and Yttrium-90 Ibritumomab Tiuxetan.

Under this authorization, you are approved to manufacture Ibritumomab Tiuxetan, Yttrium-90, and the kits for the preparation of Indium-111 Ibritumomab Tiuxetan and Yttrium-90 Ibritumomab Tiuxetan. Ibritumomab bulk will be manufactured at your facility in San Diego, California. Ibritumomab Tiuxetan and the non-biological kit components will be manufactured, filled, labeled, and packaged into kits at [redacted] In accordance with approved labeling, your product will bear the proprietary name Zevalin and will be marketed as two single-dose kits for radiolabeling with Indium-111 and Yttrium-90, each containing a 3.2 mg vial of Ibritumomab Tiuxetan, a 2 mL vial of 50 mM sodium acetate buffer, a 10 mL vial of formulation buffer and a sterile, empty reaction vial. The Yttrium-90 Chloride Sterile Solution will be manufactured and distributed under contract by MDS Nordion, Ottawa, Ontario, Canada.

The dating period for Ibritumomab Tiuxetan drug product shall be 24 months from the date of manufacture when stored at 2 to 8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated bulk. The expiration date for the kit shall be 24 months or less, dependent on the shortest expiration date of any of the components, when stored at 2 to 8°C. The dating periods of the non-biological kit components when stored at 2 to 8°C, shall be 24 months for sodium acetate buffer, 30 months for formulation buffer, and 30 months for the reaction vials. The dating period of the Yttrium-90 Chloride Sterile Solution shall be 5 days when stored at 15 to 30°C. The Ibritumomab bulk may be stored for up to [redacted] months at [redacted]

Results of ongoing stability studies should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots of each product. The stability protocols in your license application are considered approved for the purpose of extending the expiration dating period of your Ibritumomab Tiuxetan drug product, Ibritumomab bulk, and the non-biological kit components as specified in 21 CFR 601.12.

You are not currently required to submit samples of future lots of Ibritumomab Tiuxetan or the kit to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay and release of only those lots that meet release specifications.

Any changes in the manufacturing, testing, packaging or labeling of Ibritumomab Tiuxetan, the kits, or Yttrium-90 Chloride Sterile Solution, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval consistent with 21 CFR 601.12.

As requested in your letter of October 9, 2001, marketing approval of this product for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma, other than those patients with Rituximab-refractory, follicular NHL, is granted under the accelerated approval for biological products regulations, 21 CFR 601.40-46. These regulations permit the use of certain surrogate endpoints or an effect on a clinical endpoint other than survival or irreversible morbidity as bases for approval of products intended for serious or life-threatening illnesses or conditions.

Approval under these regulations requires that you conduct adequate and well-controlled studies to verify and describe the clinical benefit attributable to this product and that such studies be carried out with due diligence. If the postmarketing studies fail to verify that clinical benefit is conferred by Ibritumomab Tiuxetan, or the clinical studies are not conducted with due diligence, the Agency may, following a hearing, withdraw or modify approval to the extent that approval rests on the surrogate endpoint data.

Granting of this approval is contingent upon completion of clinical studies, as outlined in your commitment of December 12, 2001, designed to do the following:

1. To verify the clinical benefit and further assess the safety and efficacy of Zevalin radioimmunotherapy in patients with chemotherapy relapsed or refractory follicular non-Hodgkin's lymphoma (NHL). This will be assessed in a randomized, multicenter study to establish the net clinical benefit of the Zevalin therapeutic regimen used in combination with Rituxan as compared to Rituxan therapy alone. For this study, the primary efficacy variable will be event-free survival defined as absence of disease progression, initiation of additional lymphoma therapy, or death from any cause. Uniform criteria will be used to define when additional anti-lymphoma treatment is initiated including the presence of disease-related symptoms, threatened end-organ

function, cytopenias secondary to NHL, massive bulk disease, or steady disease progression over at least 6 months without meeting the definition of progressive disease. The final protocol will be submitted to CBER by May 30, 2002. Completion of subject accrual and the study are anticipated by November 30, 2004 and May 30, 2006, respectively. A final clinical study report will be submitted to CBER by August 30, 2006.

2. To verify the clinical benefit and further assess the safety and efficacy of the Zevalin therapeutic regimen in patients with transformed CD20+ B-cell NHL. For this study, the primary efficacy variables will be overall response rate and duration of response. Other measures of clinical benefit will include event-free survival, time to progression, and quality of life and disease-related symptoms, including B symptoms. The final protocol will be submitted to CBER by May 30, 2002. Completion of subject accrual and the study are anticipated by November 30, 2004 and November 30, 2005, respectively. A final clinical study report will be submitted to CBER by February 28, 2006.

3. To continue to assess patients enrolled in Study —— and —— for progression-free (PFS) and overall survival (OS). Patient follow-up data will be collected every 6 months, until the time to progression data has matured. The first of these data assessments will be submitted to the IND by May 30, 2002. An addendum to the —— and ——; final study reports providing the results of comparative analyses of PFS and OS will be submitted to CBER three months after the final analysis. The projected date for the final clinical report to be submitted to CBER is November 30, 2002.

Design, initiation, accrual, completion, and reporting of these studies are expected to occur within the framework described in your letter of December 12, 2001. It is understood that, to fulfill the requirements of accelerated approval, the above studies must be appropriately designed and conducted with due diligence and must demonstrate clinical benefit.

In addition, we acknowledge the following agreed upon post-approval commitments, as described in your letters of December 12, December 18 and December 20, 2001 and February 14, 2002:

4. To continue assessment of the immunogenicity of the Zevalin therapeutic regimen by long-term monitoring for human anti-chimeric and human anti-murine antibody response in subjects enrolled in all Zevalin studies under any IDEC-sponsored IND including the post-approval commitment studies listed under items 1 and 2 of this letter. Interim data on immunogenicity will be submitted annually to the IND(s) and a final report will be submitted by August 30, 2006.

5. To continue long-term monitoring of subjects to determine the incidence of myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML). This monitoring will be conducted in all Zevalin studies under any IDEC-sponsored IND,

including the post-approval commitment studies listed under items 1 and 2 of this letter. Interim data on MDS and AML will be submitted annually to the IND(s) and a final report will be submitted by August 30, 2006.

6. To perform a suitable extraction study with the Ibritumomab bulk in the ——— ——— container, as described in your response to the Agency's pre-approval inspectional observations. The study will be completed by June 30, 2002 and the results submitted to CBER in the next annual report.

It is requested that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). All adverse experience reports should be prominently identified according to 21 CFR 600.80 and be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

You are required to submit reports of biological product deviations in accordance with 21 CFR 600.14. All manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution, should be promptly identified and investigated. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, a report must be submitted on Form FDA-3486 to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 2567. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels).

As specified in 21 CFR 601.45, you are required to submit any promotional materials that contain information relating to an accelerated approval indication to CBER, for review and approval, at least 30 days prior to the initial publication of any advertisement or to the initial dissemination of any promotional labeling. You may also submit draft copies of proposed introductory advertising and promotional labeling that only contain information related to Zevalin for the treatment of Rituxan-refractory follicular, non-Hodgkin's lymphoma, for review. In addition, all final printed advertising and promotional labeling should be submitted at the time of initial dissemination. Promotional materials should be submitted with an FDA Form 2567 or Form 2253 to the Advertising and Promotional Labeling Branch, HFM-602, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other products should be made

unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Sincerely yours,

Jay P. Siegel, M.D., FACP
Director
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research